The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: FPAA672PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/IN2005/000125	25 April 2005 (25.04.2005)	28 April 2004 (28.04.2004)

Title of invention
PROCESS FOR THE PREPARATION OF TELITHROMYCIN

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
ALEMBIC LIMITED
Alembic Road, Gujarat,
390 003 Vadodara
India

Telephone No.: +91 265 230 7423
Facsimile No.: +91 265 228 2931
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
SOHANI, Suhas
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
DEODHAR, Mandar
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/IN2005/000125

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PATEL, Nishant
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PATEL, Manish
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DAVADRA, Mahesh
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KANSAL, Vinodkumar
Alembic Limited, Alembic Road, Gujarat,
390 003 Vadodara
India

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	IN

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/IN2005/000125

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MAJUMDAR, Subhatosh
GANGULI, Dr., Sanchita
SANDU, Ashwini
KUMAR, Raju
SEN, Abhishek

S. Majumdar & Co.
5, Harish Mukherjee Road
700 025 Calcutta
India

Telephone No.
+91 33 2455 7484

Facsimile No.
+91 33 2455 7487

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of the applicable time limit under Rule 69.1(d).

4. ☐ The applicant expressly wishes the international preliminary examination **to start earlier** than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

See Notes to the demand form

Sheet No. . 4

International application No.
PCT/IN2005/000125

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	7 sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to a sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Sanchita Ganguli

GANGULI, Dr., Sanchita
Registration No. IN/PA-625

Place: Calcutta Date: 25-01-2006

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

ce Notes to the demand form

S. MAJUMDAR & CO.
PATENT & TRADEMARK ATTORNEYS

Undertakings : Intellectual Property Laws
Patents, Trademarks, Designs, Copyrights
Licencing, Investigations, Litigations
DOMESTIC AND INTERNATIONAL

5, Harish Mukherjee Road, Kolkata-700 025
Tel : 91-33-2455 7484/85/86, Fax : 91-33-2455-7487/88, E-mail : cal@patentindia.com

The International Preliminary Examining Authority
European Patent Office
D-80298
Munich

Via Fax & Courier
00 49 89 2399 4465

January 25, 2006

Dear Sirs

Re : **RESPONSE TO WRITTEN OPINION UNDER RULE 66.3**
PCT International Application No. PCT/IN2005/000125
International Filing Date : 25-04-2005
Applicant : ALEMBIC LIMITED et al
Title : PROCESS FOR THE PREPARATION OF TELITHROMYCIN
Priority : 491/MUM/2004 dated 28-04-2004
Agents' File Ref. : FPAA672PCT

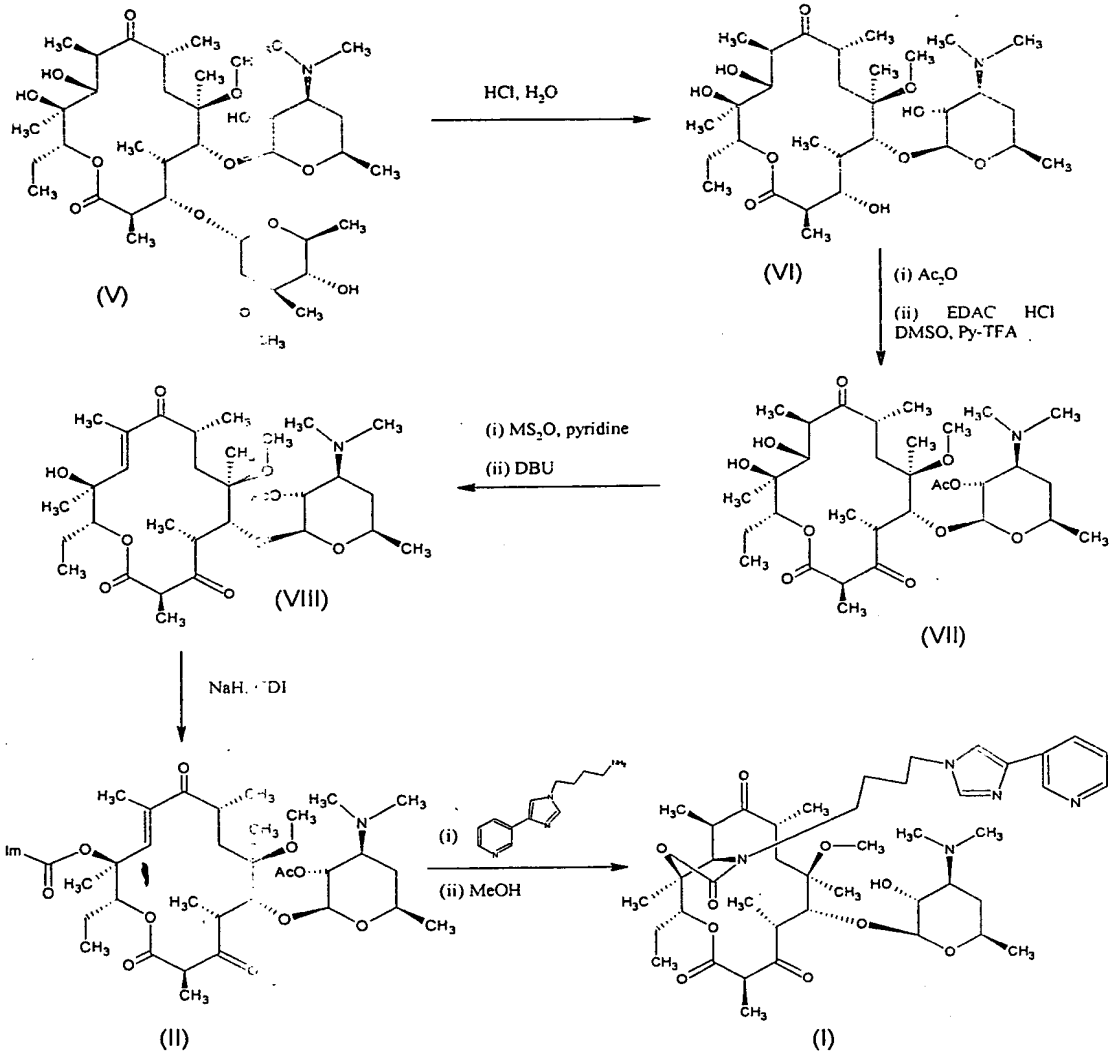
Please refer to the International Search Report and Written Opinion issued by the International Searching Authority, European Patent Office, date of mailing November 25, 2005. The applicants respectfully submit that they do not agree with the opinion and submit arguments as under which may please be considered as response to the Written Opinion:

In view of the citation, D1 (XP 009056485) referred to in the Written Opinion as the closest prior art of the present invention and rendering the present invention obvious, the applicants do not agree with the same and propose to submit the arguments as under:

D1 has been acknowledged in the present application (page 3 to 4 of the publication WO 2005/105821)

D1 describes the process for the preparation of various ketolides, including Telithromycin in which Clarithromycin (formula V) is reacted with hydrochloric acid to remove cladinose ring at C-3 position (formula VI) followed by selective acetylation of the 2'-hydroxy group in formula VI and selective oxidation of the 3-hydroxy group generated ketolide of formula VII. Further, 11-hydorxy group of compound of formula (VII) is selectively mesylated followed by base induced β- elimination to furnish α,β-unsaturated ketone (formula VIII). The compound of formula (VIII) is further treated with sodium hydride and carbonyldiimidazole to form 12-O-acyl imidazole of formula (I), which upon stereoselective cyclization with (4-(3-pyridinyl)-imidazol-1-yl)-butylamine and subsequent deprotection of the 2'-hydroxy group gives Telithromycin of Formula (I). This process is outlined in following Scheme:

Contd. Page 2



It is respectfully submitted that the cited art process starts with hydrolysis to form free –QH group at third position. This leads to formation of compound with two free –OH groups which results in formation of impurities. Though the steps of use of acid and use of carbonyl diimidazole and deprotection of the 2' acetyl group are common to that of the present invention but the sequence of the steps is not the same and neither is the end result similar except for arriving at telithromycin by the process.

Further, the process described in D1 suffers with several disadvantages such as use of reagents like NaH

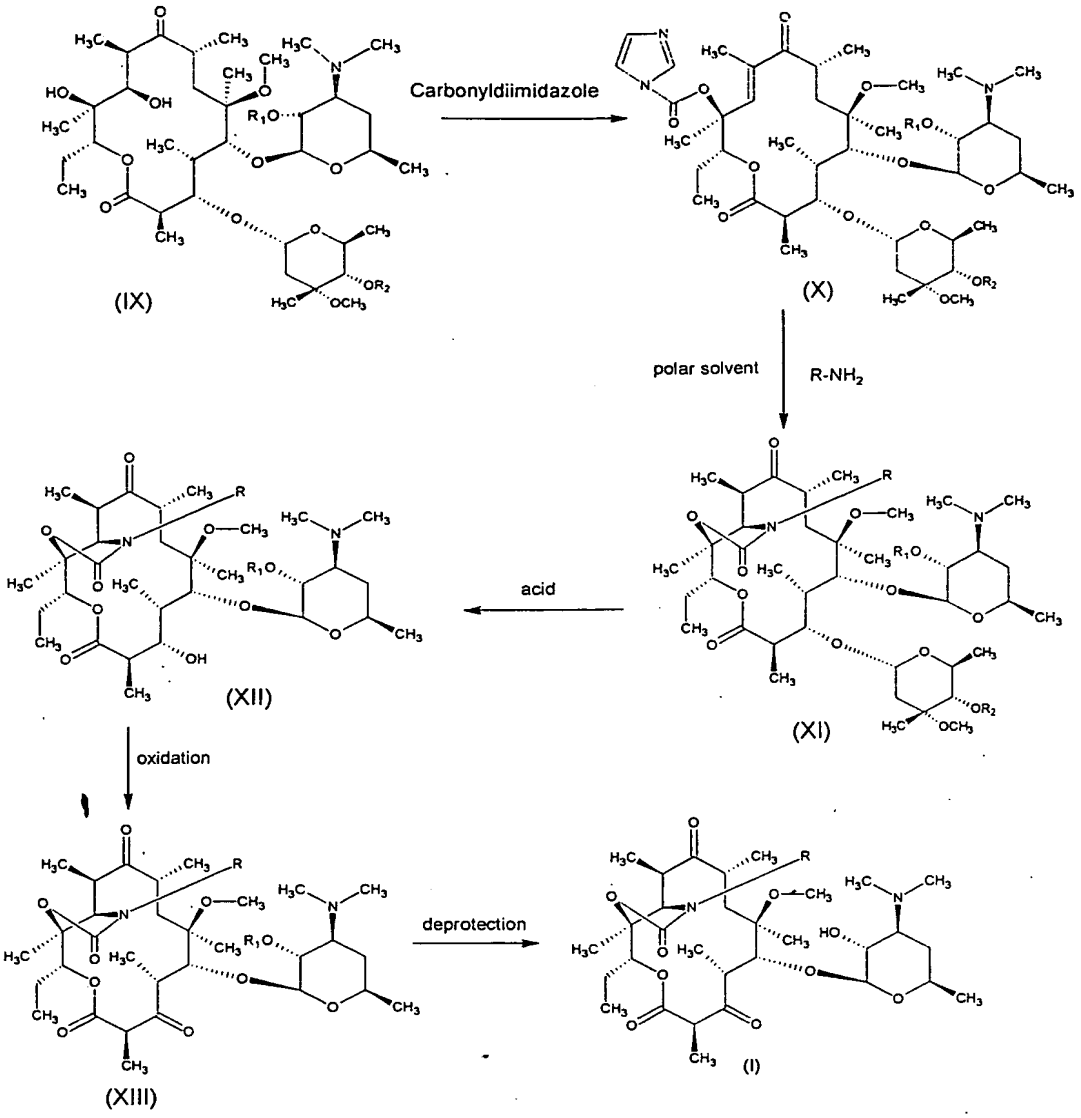
The reagent like NaH is pyrophoric in nature and it is highly prone to hazard and is difficult to handle at an industrial scale.

Contd. Page 3

Therefore, present inventors have found a process which not only overcomes the drawbacks of prior art but provides Telithromycin of high purity(more than 99%). Moreover, the sequence of steps involved in the present invention are different and so are the intermediate products. It is respectfully pointed out that the intermediate products are not only different from that of the cited art but they are novel given the teachings of D1 as well as other known art in the field.

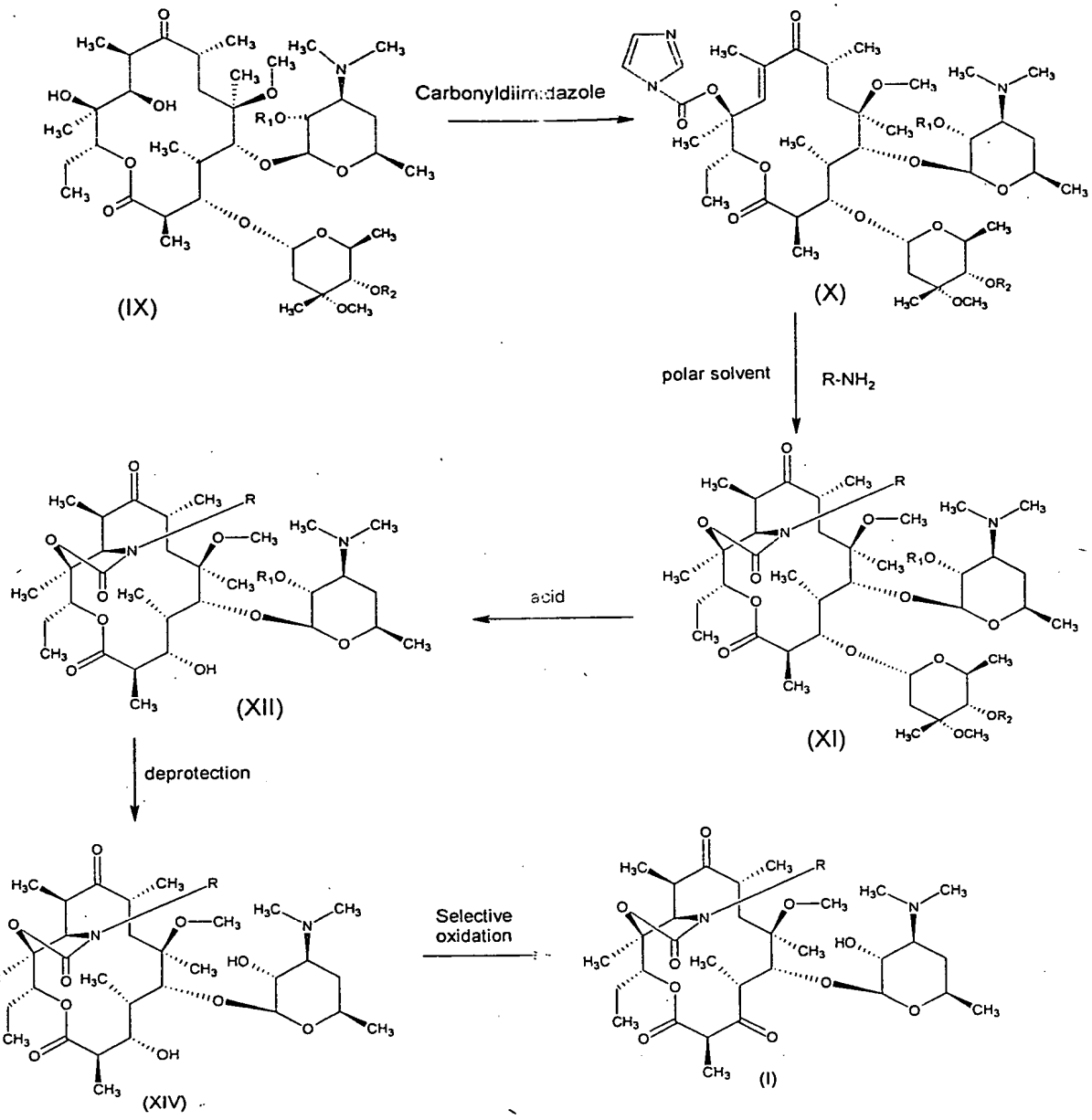
The present invention relates to the process for the preparation of Telithromycin which comprises reaction of 2',4"-di-O-benzoyl-6-O-methylerythromycin A with carbonyldiimidazole in presence of solvent and base followed by condensation with 4(4-(3-pyridinyl)-imidazol-1-yl)-butylamine in polar solvent which is further reacted with hydrochloric acid to remove cladinose ring at C-3 position and furthermore, selective oxidation of the 3-hydroxy group generated ketolide then deprotection of the 2'-hydroxy group gives Telithromycin. This process is outlined in following Scheme:

Contd. Page 4



The present invention also relates to another embodiment which depicted in the following scheme:

Contd. Page 5



On the other hand, D1 starts with hydrolysis of clarithromycin hydrolysis, followed by acetylation and selective oxidation whereas the present invention starts with coupling of clarithromycin with carbonyldiimidazole in the presence of a polar solvent and a base to provide a novel intermediate of formula X. This step is entirely different and is not even remotely suggested by the closest prior art D1.

Contd. Page 6

As mentioned above, D1 mentions the steps of use of hydrochloric acid carbonyl diimidazole and deprotection in context with other starting material and end product. In other words, these are used in different steps/sequence of the process of D1. There is no mention or motivation that carbonyl diimidazole may be used in a coupling reaction along with defined polar solvent and base. On the contrary, it is used along with sodium hydride to form 12 O-acyl imidazolide. Taking cue from the same, it would not be possible for a person skilled in the art to use carbonyl diimidazole in a coupling reaction with defined polar solvent and base to form intermediate compound of present invention which would ultimately lead to the formation of telithromycin. There is no lead or motivation in D1 that sequence steps could be changed to form novel intermediates of present invention and ultimately lead to formation of telithromycin. For this citation to lead to the present invention by altering sequence of steps there ought to be some motivation in the same to alter sequence steps with different reactants and yet reach the present invention. In absence of such motivation or lead it is not possible to comprehend that reaction sequence may be altered, reactants differed and distinct intermediates to be formed and achieve the formation of telithromycin.

Moreover, it cannot be said that the process steps have been exactly reversed. Only the carbonyl diimidazole is added in the first step and acid in the third step in place of D1 where acid is added in first step and carbonyl diimidazole is added in fourth step that too along with NaH. To use carbonyl diimidazole in the first step for coupling reaction in presence of polar solvent and base to obtain compound of formula X is itself novel and inventive. There is no clue/motivation in D1 that carbonyl diimidazole could be used in the first step and the use of NaH can be avoided and yet a compound of formula X (as well as novel compound of XIa) which is different from compound 4 of D1 could be achieved which after different steps would ultimately lead to telithromycin.

The introduction of the group R of present invention in step (b) by condensation with RNH_2 in suitable polar solvent cannot be equated or motivated with the cyclization in the last step of D1 since the start and end compounds are different. If teaching of use of RNH_2 for condensation is taken to render the process step obvious vis-à-vis D1 though the same uses it in a different step, use of RNH_2 in any reaction would be rendered obvious by teachings in basic chemistry since the use of RNH_2 is not new. It is the process step in which a specific reagent is used to render a specific product which makes it new and inventive and not the use of the reagent only. In this perspective D1 teaches few reagents which are used in the present process but not with same start material or intermediate products.

Accordingly, it cannot render the present invention obvious since neither the process steps nor similar start and end product of each step is taught or motivated. It cannot be indicated that the present invention is merely reversal of the process steps of D1 in view of the above.

Even if for argument sake it is accepted that the process steps are reversed there is no motivation/teaching in the cited art that the process steps may be reversed, different reagents be used, use of NaH could be avoided and yet telithromycin may be achieved along with novel intermediate products.

Contd. Page 7

There is no guarantee that in chemical reaction process steps could be reversed and the same product would be reached, rather it is against the general knowledge in the field that reversal of process steps could lead to the same product. Thus even if it is taken that the process steps are reversed the teachings of D1 would go against that of the present invention since there is no motivation that reversal of process steps would lead to same result rather it teaches away/opposite from the same.

As to the intermediates, it is respectfully submitted that none of the novel intermediates namely Xa, XIa XIIa and XIIIa are taught/motivated from the cited art since none of the intermediates in D1 have the R-N group attached. From the teachings of the D1 it is not possible for a persons skilled in the art to comprehend the compounds intermediates Xa, XIa XIIa and XIIIa.

It is thus respectfully submitted that it would need ingenuity of thought to start with different process steps and avoid the use of NaH and form the intermediates as of present invention and mere trial and error would not reach the same. It is reiterated that the present invention teaches away from the cited art.

Thus the present invention teaching a cost effective, easy to operate on large scale process without the use of compounds like NaH and resulting in telithromycin which does not require further cumbersome process of purification is neither taught nor motivated from the cited art.

It is reiterated that the intermediates formed by the method of present invention are novel and inventive vis-à-vis D1 since it is not possible to comprehend the formation of such products without ingenuity of thought.

The above may be taken as response to the Written Opinion and a favorable IPER may be used. Should further requirements, clarifications remain, the applicants request the issuance of a second Written Opinion.

Sincerely yours

Ganguli

DR. SANCHITA GANGULI
Of S. MAJUMDAR & CO.
Applicants' Agent